IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Re: Appeal to the Board of Patent Appeals and Interferences

Appellant: Xuedong Song	)	Examiner: Jacqueline A. DiRamio
Appl. No: 10/718,989	)	Art Unit: 1641
Filed: November 21, 2003	)	Deposit Acct. No: 04-1403
Title: Membrane-Based Lateral Flow Assay Devices That Utilize Phosphorescent Detection	)	Confirmation No: 9109
	)	Customer No: 22827

1. ☐ **NOTICE OF APPEAL**: Pursuant to 37 CFR 41.31, Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Examiner twice/finally rejecting claims _____.

2. ☒ **BRIEF** on appeal in this application pursuant to 37 CFR 41.37 is transmitted herewith (1 copy).

3. ☐ An **ORAL HEARING** is respectfully requested under 37 CFR 41.47 (due within two months after Examiner's Answer).

4. ☐ Reply Brief under 37 CFR 41.41(b) is transmitted herewith (1 copy).

5. ☐ "Small entity" verified statement filed: [ ] herewith [ ] previously.

6. **FEE CALCULATION:**

	Fees
If box 1 above is X'd enter $ 510.00	$ .00
If box 2 above is X'd enter $ 510.00	$ 510.00
If box 3 above is X'd enter $1,030.00	$ .00
If box 4 above is X-d enter –0- (no fee)	$ .00

PETITION is hereby made to extend the original due date of May 12, 2008, hereby made for an extension to cover the date this response is filed for which the requisite fee is enclosed (1 month $120; 2 months $460; 3 months $1,050; 4 months $1,640, 5 months $2,230 $ 460.00

SUBTOTAL: $ 970.00

Less any previous extension fee paid since above original due date. - $ 0.00

SUBTOTAL: $ 970.00

If "small entity" verified statement filed ☐ previously, ☐ herewith, enter one-half (½) of subtotal and subtract - $ .00

TOTAL FEE ENCLOSED: $ 970.00

☐ Fee enclosed.

☐ Charge fee to our Deposit Account/Order Nos. in the heading hereof (for which purpose one additional copy of this sheet is attached)

☒ Charge to credit card (attach Credit Card Payment Form – PTO 2038)

☐ Fee NOT required since paid in prior appeal in which the Board of Appeals did not render a decision on the merits.

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Date: July 14, 2008

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PATENT
ATTORNEY DOCKET NO: KCX-741 (19044)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

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Honorable Commissioner for Patents
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BRIEF ON APPEAL

Honorable Commissioner:

Appellant submits the following Brief on Appeal in accordance with 37 C.F.R. § 41.37:

1. REAL PARTY IN INTEREST

The real party in interest in this matter is the Assignee of record, Kimberly-Clark, Worldwide, Inc.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellant or the Appellant's legal representative which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 64-85 and 89-92 are currently pending in the captioned application, including independent claim 64. Claims 1-63 and claims 86-88 have been previously canceled. All of the claims involved in this Appeal are attached hereto in the Claims Appendix.

Claims 64-85 and 89-92 stand rejected. The rejections of claims 64-85 and 89-92 are hereby appealed.

4. STATUS OF AMENDMENTS

To the Appellant's knowledge, all amendments have been entered into the record.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 64 is directed to a method for detecting an analyte within a test sample (p. 2, l. 9-10). The method includes providing a lateral flow assay device that comprises a porous membrane (p. 2, ll. 11) in fluid communication with phosphorescent particles conjugated with a specific binding member (p. 10, ll. 17-23). The phosphorescent particles comprise a phosphorescent label encapsulated within a matrix (p.8, ll. 19-23). The phosphorescent label of the phosphorescent particles emitting a detection signal having an emission lifetime of about 1 microsecond or more following excitation of the phosphorescent label (p. 15, ll. 21-23). The phosphorescent label also having a Stokes shift of greater than about 100 nanometers (p. 16, ll. 10-13). In addition, the porous membrane defines a detection zone within which is immobilized a capture reagent (p. 2, ll. 27-30).

The method of claim 64 further includes contacting the lateral flow assay device with the test sample (p. 6, ll. 17-19), subjecting the detection zone to illumination pulses

to generate the detection signal (p. 14, ll. 24-32), and thereafter, measuring the intensity of the detection signal, wherein the amount of the analyte within the test sample is proportional to the intensity of the detection signal (p. 21, ll. 10-13).

Dependent claim 78 adds to independent claim 64 the further limitation that the intensity of the detection signal is measured from about 1 to about 100 microseconds after the detection zone is subjected to one or more pulses of illumination (p. 15, ll. 5-9).

Dependent claim 81 adds to independent claim 64 the further limitation that the intensity of the detection signal is measured by a time-gated detector (p. 16, ll. 18-25).

Dependent claim 85 adds to independent claim 64 the further limitation that the porous membrane further defines a calibration zone within which a calibration capture reagent is immobilized (p. 13, ll. 5-13), and dependent claim 92 further limits claim 85 in that the calibration capture reagent comprises a polyelectrolyte (p. 13, ll. 17-18).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the Final Office Action, claims 64-77, 79, 80, and 82-84 were rejected under 35 U.S.C. §103(a) as being unpatentable over Daniels, et al. (U.S. Patent Application Publication No. 2002/0004246) in view of Klimant (U.S. Patent No. 6,770,220), and in light of O'Riordan, et al. (*Analytical Biochemistry*, **290**, 366-375 (2001)).

In the Final Office Action, claims 78 and 81 were rejected under 35 U.S.C. §103(a) as being unpatentable over Daniels, et al. in view of Klimant, and further in view of Zarling, et al. (U.S. Patent No. 5,674,698).

In the Final Office Action, claims 85 and 89-91 were rejected under 35 U.S.C. §103(a) as being unpatentable over Daniels, et al. in view of Klimant, and further in view of Rylatt, et al. (PCT Patent Application Publication No. WO 97/09620).

In the Final Office Action, claim 92 was rejected under 35 U.S.C. §103(a) as being unpatentable over Daniels, et al. in view of Klimant and Rylatt, et al., and further in view of Jou, et al. (U.S. Patent No. 5,670,381).

7. ARGUMENT

I. Claims 64-77, 79, 80, and 82-84 patentably define over Daniels, et al. in view of Klimant, and in light of O'Riordan, et al.

Daniels, et al. relates to immunochromatographic test strips in which multiple analytes can be detected simultaneously by using more than one semiconductor nanocrystal as a detectable label, each of which emits at a distinct wavelength (p. 1, ¶ [0002]). Specifically, the assays of Daniels, et al. include semiconductor nanocrystals that have characteristic spectral emissions that can be tuned to a desired energy by varying particle size, size distribution, and/or compositions (p. 2, ¶ [0016]). The semiconductor nanocrystals are fluorescent materials (p. 2, ¶ [0018], p. 13, ¶ [0187]). Daniels, et al. defines fluorescence as the emission of light resulting from the absorption of radiation at one wavelength (excitation) followed by nearly immediate reradiation usually at a different wavelength (p. 1, ¶ [0010]). The range of excitation wavelengths of the nanocrystals is broad, which allows the use of a single energy source to effect simultaneous excitation of all populations of semiconductor nanocrystals in a system having distinct emission spectra (p. 2, ¶ [0018]). The semiconductor nanocrystals have a wavelength band of emission not exceeding about 40 nm (p. 5, ¶ [0085]), and line shapes that are symmetric, Gaussian or nearly Gaussian with an absence of a tailing region (p.2, ¶ [0017]). The ability of the semiconductor nanocrystals to produce discrete optical transition along with the ability to vary the intensity of these transitions, enables the development of a versatile and dense encoding scheme (p. 11, ¶ [0167]).

The semiconductor nanocrystals of Daniels, et al. are used as detectable labels in flow-type assay devices that utilize a suitable absorbent, porous or capillary possessing material suitable thereto (p. 8, ¶ [0126]). Hence, the detection schemes of Daniels, et al. are dry chemistry-based devices.

To detect the signals produced by the semiconductor nanocrystals of Daniels, et al., a signal collection mechanism collects light emitted from the area of the test strip suspected of containing semiconductor nanocrystals and this emission light is then projected onto detectors that convert incoming light into an electrical signal. The emitted light is then spectrally resolved to detect light within a narrow wavelength range and the magnitude of the signal detected for each semiconductor nanocrystal species is analyzed to determine the amount of analyte present (p. 15, ¶ [0214-0215]).

Klimant relates to phosphorescent micro- and nanoparticles containing luminescent substances, for example metal/ligand complexes with long luminescence decay times, in a solid matrix (specifically, polyacrylonitrile and its copolymers) so that they are shielded from ambient chemical parameters (col. 2, ll. 51-60). The micro- and nanoparticles can be used as luminescent standards for converting the luminescence intensity of other luminescent indicators that are on or in the environment of the particles into phase signal or time dependent parameters or can be used for markers for detection or determination of biomolecules (col. 5, ll. 42-52). Klimant also relates to a method for luminometric determination of a biochemical or chemical parameter using two different luminescent dyes which have different decay times, one of which being the described particles, wherein the time or phase characteristics of the resulting luminescent response are used for generating a reference parameter for determination of that parameter (col. 5, l. 53 – col. 6, l. 9). In Example 9, Klimant describes dispersal

of the phosphorescent particles in a 20 mM sample of phosphate buffer and provides the results of optical characterization of the dispersion (col. 8, Example 9 and Table 1).

O'Riordan, et al. examines the characteristics of the platinum- and palladium-coproporphyrin I *p*-isothiocyanatophenyl derivatives PtCP-NCS and PdCP-NCS (p. 367, second paragraph). Specifically, O'Riordan utilized solid-surface phosphorescent immunoassays, i.e., solution chemistry-based systems, to examine the characteristics of porphyrin-antibody conjugates that include the phosphorescent molecular labels bound to mouse IgG (p. 368, second column). Time response fluorescence measurement were carried out with plate readers equipped with either 532 nm excitation and 650 nm emission bandpass interference filter and red-sensitive PMT, or with 390-nm excitation and 650 nm emission bandpass interference filters and standard PMT (p. 367, second column). O'Riordan also mentions that these systems tended to lose sensitivity due to oxygen quenching of phosphorescence, and the use of an excitation laser that perfectly matches the Q-band of the phosphorescent molecule could improve sensitivity (p. 374). O'Riordan also reports that water-soluble platinum(II) and palladium(II) complexes of coproporphyrin and tetracarboxyphenlporphin display long phosphorescent life times of about 0.1 and about 1.0 microsecond, respectively, and Stokes shifts exceeding 100nm (p. 366, second column).

A. A person of ordinary skill in the art, having common sense at the time of the invention, would not have reasonably looked to Klimant and O'Riordan, et al for combination with Daniels, et al. as suggested in the Final Office Action.

The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. '"Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must

be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. See *In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Accordingly, even if all elements of a claim are disclosed in various prior art references, the claimed invention taken as a whole cannot be said to be obvious without some reason given in the prior art why one of ordinary skill would have been prompted to modify the teachings of the references to arrive at the claimed invention. See e.g., *In re Regel*, 188 U.S.P.Q. 132 (C.C.P.A. 1975).

Appellant respectfully submits that the Final Office Action fails to provide adequate reasoning with some rational underpinning to support the legal conclusion of obviousness, as is required to establish a *prima facie* case of unpatentability. Specifically, Appellant submits that the Final Office Action fails to provide a factual basis that would lead one of ordinary skill in the art to modify the teachings of Daniels, et al. according to the teachings of Klimant in light of O'Riordan, as suggested in the Final Office Action, to arrive at the pending claims. Moreover, Appellant further submits that the suggested combination of references is improper.

a. The semiconductor nanocrystals of Daniels, et al. are not functionally equivalent to the luminescent particles of Klimant.

In the Final Office Action, it was stated that the semiconductor nanocrystals of Daniels, et al. would be considered functionally equivalent to the luminescent particles of Klimant because both particles provide detectable luminescent/phosphorescent signals, can be conjugated to biomolecules, and can be effectively used as markers for labeling and detecting biomolecules.

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

Moreover, official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. As noted by the court, *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "capable of such instant and unquestionable demonstration as to defy dispute" (citing *In re Knapp Monarch Co.*, 296 F.2d 230, 132 USPQ 6 (CCPA 1961)). It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. *In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21. See also *In re*

Grose, 592 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979) ("[W]hen the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, it must provide evidentiary support for the existence and meaning of that theory."); *In re Eynde*, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973) ("[W]e reject the notion that judicial or administrative notice may be taken of the state of the art. The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of such notice.").

Appellant respectfully submits that the fluorescent semiconductor nanoparticles of Daniels, et al. and the phosphorescent particles of Klimant are not equivalent. They are neither functionally nor mechanically equivalent to one another, and no documentary evidence has been provided to support the equivalency statement of the Final Office Action.

In the Final Office Action, it was stated that both particles provide detectable luminescent/phosphorescent signals. In contrast, however, the two different materials provide very different types of luminescent signals.

The semiconductor particles of Daniels, et al. are fluorescent materials that absorb radiation at one wavelength (excitation) and then, almost immediately following absorption, reradiate an emission that is generally at a different wavelength. The fluorescence lifetime is often very short. The fluorescence signal of these particles is normally not subject to significant quenching by molecules or materials in triplet states, such as oxygen. Furthermore, these semiconductor particles are crystals with surface functionalization and their particle structures are normally core-shell type structures. Moreover, because of their short fluorescence lifetime, they are not normally suitable for

time-resolved luminescence-based detection. To generate the fluorescence signal, a continuous excitation light source is normally used. There is no benefit to the use of a pulse illumination excitation light sources to obtain the fluorescence signal for such a particle. In fact, if a pulse illumination excitation light source were to be used, it very likely would reduce the detection sensitivity and drive up the cost of the system.

The phosphorescent particles of Klimant are quite different. As discussed in the captioned application, phosphorescence is the result of a three-stage process. In the first stage, energy is supplied by an external source, such as an incandescent lamp or a laser, and absorbed by the phosphorescent compound, creating excited electronic triplet states (as opposed to fluorescence, which only has a singlet excited state). In the second stage, the excited states exist for a finite time during which the phosphorescent compound undergoes conformational changes and is also subject to a multitude of possible interactions with its molecular environment. During this time, the energy of the excited states is partially dissipated, yielding relaxed states from which phosphorescence emission originates. The third stage is the phosphorescence emission stage wherein energy is emitted, returning the phosphorescence compound to its ground states. The emitted energy is lower than its excitation energy (light or laser) and thus of a longer wavelength. This shift or difference in energy or wavelength allows the emission energy to be detected and isolated from the excitation energy (p. 1, ll. 4-17).

The particle structures of Klimant consist of specific polyacrylonitrile or its copolymers as a matrix to encapsulate individual phosphorescent molecules in a homogenous distribution. These individual phosphorescent molecules can not be in a crystal, as are the semiconductor nanoparticles of Daniels, et al., or in an aggregate state, as phosphorescence will be severely quenched if the phosphorescent materials

are in such an aggregate or crystal form. Furthermore, phosphorescence normally exhibits a much longer lifetime than is seen in fluorescence and phosphorescence can be easily quenched by molecules of triplet state, such as oxygen.

Contrary to the assumption of the Final Office Action, the two types of materials are not functionally equivalent. While the semiconductor nanoparticles of Daniels, et al. provide fluorescent signals, the particles of Klimant provide phosphorescent signals, and these signals are not the same. The two different types of signals are emitted from different materials according to different physical and chemical processes; they can be detected by different detection techniques and will have different characteristics (e.g., different intensities, band widths, decay times, Stokes shift, etc.). For example, some instruments can easily detect fluorescence but not phosphorescence, and vice versa.

The fluorescent semiconductor nanoparticles of Daniels, et al. are simply not equivalent to the phosphorescent particles of Klimant and no documentary evidence has been put forth in the Final Office Action to suggest that they could be considered to be so. For at least this reason, Appellant submits that the suggested combination is improper.

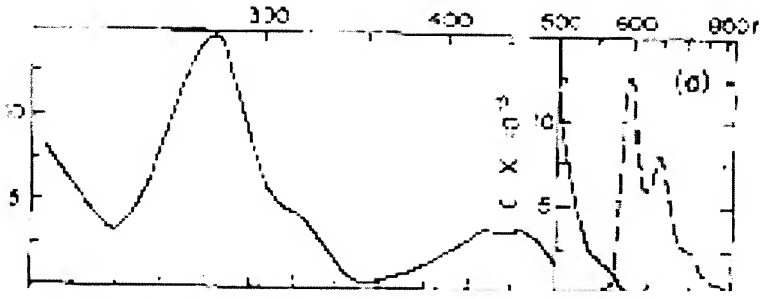
b. The references teach away from the suggested combination.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

The detection system of Daniels, et al. is effective to filter out the specific emission of the nanocrystals from all of the other electromagnetic wavelengths present at the time, including scattered light from the excitation source, as the emission is reradiated almost immediately following excitation. Hence, the emission spectra can be

spectrally resolved to differentiate the narrow emissions of specific labels and thereby provide the desired versatile and dense encoding schemes. In addition, the fluorescent materials of Daniels, et al. provide emission spectra that are not only narrow, but are also symmetric, Gaussian or nearly Gaussian with an absence of a tailing region. As described by Daniels, et al., problems with other types of luminescent materials include those due to spectral overlap that is due, in part, to the relatively wide emission spectra and the overlap of the spectra near the tailing region (p. 1, ¶ [0013]). Thus, Daniels, et al., specifically teaches away from luminescent materials that have non-symmetric emission spectra with a tailing region.

Klimant, on the other hand, utilizes phosphorescent particles that take advantage of the phosphorescence time delay of the phosphorescent particles, e.g., in developing useful reference parameters based upon the differences in phase signal and time dependence between the phosphorescent particles and other luminescent materials. These materials have long decay times, i.e., the emission spectra are neither symmetrical nor Gaussian. For example, phosphorescent materials utilized in the examples of Klimant included ruthenium compounds [(II)-tris-4,7-diphenyl-1,10 phenanthroline or ruthenium(II)-tris-1,10 phenanthroline]. The absorption and luminescence spectra of (II)-tris-4,7-diphenyl-1,10 phenanthroline ([Ru(diphenylphen)]) is shown below:



Source: Journal of the American Chemical Society, 93:13, June 30, 1971, p. 3180.

As can be seen, the emission spectra of the ruthenium phosphorescent material is not symmetric, Gaussian, or even near-Gaussian, which is clearly in contradiction to the requirements of Daniels, et al.

The two types of detection regimes utilized by the references are fundamentally different. The fluorescent materials of Daniels, et al. provide a dry chemistry-based device that can differentiate multiple simultaneous signals, all of which are produced immediately upon excitation of the fluorescent materials, while Klimant is able to differentiate signals based upon the time differential between phosphorescent particles and other luminescent materials and then utilize that time differential, for instance to develop reference parameters.

The very nature of the techniques are different, with Daniels, et al. requiring the emission of the semiconductor nanoparticles immediately following excitation and emissions that are narrow and symmetric, and Klimant requiring the long decay times and time differential provided by use of the phosphorescent materials. Daniels, et al. clearly teaches against utilization of luminescent materials that are not fluorescent and that do not provide a narrow, symmetric emission spectrum, as is required by the

reference. For at least this reason, Appellant respectfully submits that the suggested combination is improper.

c. The proposed modification of Daniels, et al. would render the invention of Daniels, et al. unsatisfactory for its intended purpose.

If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

As previously mentioned, the detection techniques of Daniels, et al. provide materials with narrow, symmetric emission spectra and utilize a signal collection mechanism that upon excitation collects light emitted from the area of the test strip suspected of containing semiconductor nanocrystals. The narrow, symmetric emission spectra are very important because the detection techniques relies on the wavelength differences between the emission spectra of the different semiconductor particles (as well as differences between the emission spectra and other interfering lights such as fluorescence of nitrocellulose membranes and scattered light) to separate the emission signals of interest from unwanted background signals. If the emission spectrum of the labeling particle is not narrow, it is not practical to achieve simultaneous detection of multiple analytes as claimed in the technique of Daniels, et al. because of the likely fluorescence overlap of one particle with other signals. For instance, it would be very difficult to differentiate the fluorescence signals from different particles and/or background noise through wavelength difference. If the emission spectrum of the labeling particle is not narrow, the detection scheme will either pick up a lot of background signal (noise) or lose a lot of emission signal of interest, significantly

reducing detection sensitivity, because of the likelihood of the overlap of the fluorescence signal with interfering background light. According to Daniels, et al. the emission light is separated by wavelength difference from particle to particle as well as from background lights through an optical filter or other techniques based on wavelength difference. The separated emission signal is projected onto detectors that convert incoming light into an electrical signal. For example, a band-pass filter is normally required to separate the emission signal of a narrow wavelength range from each semiconductor nanocrystal species and is analyzed to determine the amount of analyte present. This detection system is effective to filter out the specific emission of the targeted nanocrystals from one particle and another and as well from all of the other interfering electromagnetic wavelengths present at the time, including light from the excitation source, substrate fluorescence from porous membranes, and biological sample matrix, and the emission spectra can be spectrally resolved to differentiate the narrow emissions of specific labels and thereby provide the desired versatile and dense encoding schemes.

The particles of Klimant are phosphorescent and have long luminescent decay times. Accordingly, if the phosphorescent particles of Klimant were simply substituted for the fluorescent semiconductor nanocrystals of Daniels, et al., as was suggested in the Final Office Action, not only could the emission spectra of different particles overlap, but also the detection system of Daniels, et al. will not work optimally because the emission signal of the phosphorescent particles of Klimant is more effectively separated from the other unwanted backgrounds through lifetime difference, rather than wavelength difference as is the case for Daniels, et al. Simply, two totally different detection techniques are desired for effectively detecting the two types of particles. Accordingly,

the purpose of Daniels, et al., to provide versatile and dense encoding schemes, would not be possible were one to attempt to utilize the phosphorescent particles of Klimant in place of the fluorescent semiconductor nanocrystals.

The proposed modification of Daniels, et al. would render the invention of Daniels, et al. unsatisfactory for the intended purpose, and for at least this reason, Appellant respectfully submits that the suggested combination is improper.

Appellant emphasizes that the issue in conducting an analysis under 35 U.S.C. § 103(a) hinges on whether the claimed invention as a whole would have been obvious. In this case, the Final Office Action parsed and dissected only certain portions of Klimant and O'Riordan, et al., and then used these dissected portions in a way that would require a substantial reconstruction of Daniels, et al. Thus, for at least the reasons set forth above, Appellant respectfully submits that one of ordinary skill in the art would not have found it obvious to modify the references in the manner suggested in the Final Office Action.

B. Only improper hindsight gained from exposure to Appellant's disclosure would lead the person of ordinary skill from Daniels, et al., Klimant, and O'Riordan, et al. to the limitations of claims 64-77, 79, 80, and 82-84.

Clearly, the only incentive or motivation for modifying Daniels, et al. using the teachings of Klimant and O'Riordan, et al. in the manner suggested in the Final Office Action results from using Appellant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103. The Supreme Court has reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397.

See also, *Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474. Nevertheless, in KSR the Supreme Court also qualified the issue of hindsight by stating that "[r]igid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397.

No common sense line of reasoning has been provided that would lead one of ordinary skill in the art from the teachings of Daniels, et al. to the suggested combination with Klimant and O'Riordan, et al. Only with Appellant's specification could the structure of claims 64-77, 79, 80, and 82-84 be attained, and any attempt to arrive at the structure of claims 64-77, 79, 80, and 82-84 through study of the cited references is only reachable from improper hindsight analysis after viewing Appellant's specification.

II. Claims 78 and 81 patentably define over Daniels, et al. in view of Klimant, and further in view of Zarling, et al.

Zarling, et al. provides labels, detection methods, and detection apparatus which permit ultrasensitive detection of cells, biological macromolecules, and other analytes. The labels of Zarling, et al. are up-converting labels that are characterized by excitation and emitted wavelengths that are typically in the infrared or visible portions of the spectrum (col. 5, ll. 23-30). Specifically, the luminescent materials of Zarling, et al. are capable of multiphoton excitation (col. 5, ll. 40-43). Multi-photon imaging utilizes luminescent materials that can simultaneously absorb two or more photons to arrive at an excited energy state at which the material can emit a detectable signal in the visible or near-visible spectrum. Multi-photon absorption is possible through focus of a high photon density pulse on the luminescent material. The requisite high photon density is achieved through focusing a high intensity, long wavelength energy pulse on the target

as described, for example, in U.S. Patent Nos. 5,034,613 to Denk, et al. and 6,166,385 to Webb, et al. Accordingly, the method can utilize long wavelength excitation energy in near-infrared and infrared (IR) spectrum.

The biochemical assay methods described by Zarling, et al. include *in situ* hybridization, Northern or Southern blot, or in solution hybridization assays (col. 21, ll. 3-6). Zarling, et al. describes utilization of the materials in an assay utilizing a microtiter plate reader (col. 39, l. 10 – col. 40, l. 4), in flow cytometry (col. 42, ll. 31-49), and in other solution-based assays (see, e.g., col. 51, l. 16 – col. 52, l. 56). Zarling, et al. does not disclose or suggest utilization of the materials in a dry chemistry-based system such as a lateral flow system.

Because the system utilizes multi-photon excitation materials and methods, the excitation and emission detection regimes must be specific for these materials. For instance, the illumination of a sample includes use of optical filters that have high transmissibility in the excitation wavelength ranges and low transmissibility in one or more undesirable wavelength bands (col. 31, ll. 52-60). Due to the nature of multiphoton excitation, the samples must also be provided with the excitation energy at suitably high density. Furthermore, the wavelength of the emission signal of interest from multiphoton excitation is shorter than the excitation wavelength, which is opposite to the fluorescence of the semiconductor particles of Daniels, et al. and the phosphorescent particles of Klimant.

A. A person of ordinary skill in the art, having common sense at the time of the invention, would not have reasonably looked to Zarling, et al for combination with Daniels, et al. as suggested in the Final Office Action.

The systems of Daniels, et al. and Zarling, et al. are extremely different. For instance, in addition to the differences discussed previously, with reference to the fluorescent semiconductor nanoparticles of Daniels, et al. and phosphorescent materials in general, the luminescent materials of Zarling, et al. are also up-converting phosphorescent materials that are excited to luminescence via multiphoton excitation. The excitation requirements, the detection regimes, and the analysis techniques necessary for these materials are different. For instance, both excitation and emission of multi-photon excited phosphorescent materials generally takes place in the IR, near-IR, or visible spectrum, with the emission wavelengths at higher energy (shorter wavelength) than the excitation wavelengths. This is exactly the opposite of the requirements for a single photon down-converting fluorescent material such as the semiconductor quantum dots of Daniels, et al., in which excitation is generally in the UV spectrum, and the emission is near to or slightly below the excitation (p. 5, ¶ [0086]). Given Daniels, et al., one of ordinary skill in the art would simply not look to a reference such as Zarling, et al. that teaches multiphoton excitation of phosphorescent materials in solution-based detection chemistries for information on modifying the primary reference.

The Final Office Action has parsed and dissected only certain portions of Zarling et al., and then used these dissected portions in a way that would require a substantial reconstruction of Daniels, et al., which is improper under 35 U.S.C. §103.

B. Only improper hindsight gained from exposure to Appellant's disclosure would lead the person of ordinary skill from Zarling, et al., Daniels, et al., and Klimant to the limitations of claims 78 and 81.

Clearly, the only incentive or motivation for modifying Daniels, et al. using the teachings of Klimant and Zarling, et al. in the manner suggested in the Final Office Action results from using Appellant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103. No common sense line of reasoning has been provided that would lead one of ordinary skill in the art from the teachings of Daniels, et al. to the suggested combination with Klimant and Zarling, et al. Only with Appellant's specification could the structure of claims 78 and 81 be attained, and any attempt to arrive at the structure of claims 78 and 81 through study of the cited references is only reachable from improper hindsight analysis after viewing Appellant's specification.

III. Claims 85 and 89-91 patentably define over Daniels, et al. in view of Klimant, and further in view of Rylatt, et al.

Appellant respectfully submits that dependent claims 85 and 89-91 are patentable over the suggested combination of Daniels, et al., Klimant, and Rylatt, et al. for at least the reason that these claims depend from an allowable independent claim, as discussed above with reference to the discussion of the 35 U.S.C. §103(a) rejection of independent claim 64.

IV. Claim 92 patentably defines over Daniels, et al. in view of Klimant and Rylatt, et al., and further in view of Jou, et al.

Rylatt, et al. describes a lateral flow assay device that includes a calibration zone. Specifically, the calibration zone includes therein a non-diffusibly attached calibration agent receptor capable of binding the calibration agent (p. 5, ll. 13-15). The

device also includes a test zone within which is non-diffusibly attached an analyte receptor capable of binding the target analyte (p. 5, ll. 2-4). The analyte receptor is described as a specific binding partner of the analyte (p. 8, ll. 2-5) and the calibration agent receptor is capable of participating in the formation of an immobilized specific binding pair with the calibration agent (p. 10, ll. 27-30).

Jou, et al. discloses a sandwich assay in which a soluble capture reagent can include an analyte-specific binding member that has been bound to a charged substance. The capture reagent is contacted with a test sample suspected of containing an analyte and an indicator reagent. The indicator reagent includes a first specific binding member and a detectable label. Upon one- or two-step mixing, a binding reaction results in the formation of a capture reagent/analyte/indicator complex. This complex is then in solution and still in the reaction mixture. The assay also includes the step of separation of the complex from the reaction mixture by using a solid phase that is either oppositely charged with respect to the capture reagent or that retains a second oppositely charged substance. (Col. 22, ll. 29-62.) The assay can be performed in a porous solid phase material (col. 24, ll. 52-54). The porous material can include a reaction zone containing the second charged substance such that the capture reagent and complexes thereof are immobilized in the reaction zone by the interaction of the two oppositely charged substances (col. 6, ll. 37). Jou, et al. does not describe or suggest a calibration zone on the devices.

A. A person of ordinary skill in the art, having common sense at the time of the invention, would not have reasonably looked to Jou, et al. for combination with Daniels, et al., Klimant and Rylatt, et al as suggested in the Final Office Action.

a. The proposed modification of Daniels, et al. would render the invention of Daniels, et al. unsatisfactory for its intended purpose.

When considering a sandwich-type assay, there are three components involved that form the 'sandwich.' The first component includes a binding agent that can specifically bind an analyte and also includes a detectable label. Jou, et al. has termed this first component an indicator reagent; Rylatt, et al. has termed this component an analyte detection agent; and Daniels has termed this component a first detection reagent. The second component of the sandwich is the analyte of interest. The third component of the sandwich includes a second specific binding member for the analyte (or alternatively for the complex formed between the analyte and the first component). Jou, et al. has termed this third component a capture reagent that includes a first charged substance conjugated to the second specific binding member; Rylatt, et al. has termed this component an analyte receptor; and Daniels, et al. has termed this component the capture reagent.

In Rylatt, et al. and Daniels, et al., the third component of the assay is immobilized on the membrane, in the test zone of Rylatt, et al. and in the capture region of Daniels, et al. In Jou, et al., this third component of the assay is contained in the reaction mixture. Hence, upon formation of the sandwich in Jou, et al., the sandwich is likewise contained within the reaction mixture. Jou, et al. includes a fourth component that is a second charged substance. The second charged substance has the opposite charge of the capture reagent charged substance. This second charged substance

serves to enhance the immobilization of the sandwich on the membrane. This second charged substance, however, is not in any way involved in the primary binding or detection mechanism of an analyte, it is merely a secondary component that helps to immobilize the already-formed sandwich.

With regard to other zones of the various devices, Daniels, et al. also describes a control zone, which can include immobilized therein a control reagent capable of specifically binding detection reagent that is unbound to the corresponding analyte of interest (col. 8, ¶ [0117]- [0018]), and Rylatt, et al. also describes a calibration zone, which can include therein a calibration agent receptor that is capable of participating in the formation of an immobilized specific binding pair with the calibration agent (p. 10, ll. 27-30).

In the Final Office Action, it was suggested that it would have been obvious to include with the detection method of Daniels, et al., Klimant, and Rylatt, et al. a polyelectrolyte as the capture reagent in the control region (calibration zone) as taught by Jou, et al. However, as discussed above, the polyelectrolyte of Jou, et al. that is on the membrane (the second charged substance) is not the capture reagent, but merely binds the capture reagent that is in the reaction mixture. If an immobilized component of either Daniels, et al. or Rylatt, et al. (Klimant does not describe such materials or devices), whether it be the analyte receptor of Rylatt, et al., the capture reagent of Daniels, et al. (both of which specifically bind the analyte or a complex thereof), the control reagent of Daniels, et al. (which binds unbound detection reagent), or the calibration agent receptor of Rylatt, et al. (which binds the calibration agent), were to be replaced by the second charge substance of Jou, et al., the devices would simply not function.

The second charged substance of Jou, et al. does not specifically bind any component of an assay. It merely helps to immobilize the formed detection sandwich that is in the reaction mixture. The second charged substance of Jou, et al. can not specifically bind an analyte or complex thereof, nor can it specifically bind unbound detection reagent, as in the control zone of Daniels, et al., nor can it specifically bind calibration agent, as in the calibration zone of Rylatt, et al. It is merely a fourth component that can help immobilize the entire sandwich complex that has been formed in solution. The replacement of any of the immobilized components of Daniels, et al. or Rylatt, et al. with the second charged substance of Jou, et al. would result in the loss of the desired specific binding capability in the modified device, because the materials that were previously bound to the membrane through specific binding with their respective immobilized binding partners, would not specifically bind the second charged substance of Jou, et al. Thus, the suggested modification would render the modified device unsatisfactory for its intended purpose. For at least this reason, Appellant respectfully submits that the suggested combination is improper.

B. Even if combined, the suggested combination of Jou, et al. with Daniels, et al., Klimant, and Rylatt, et al., fails to teach or suggest limitations of claim 92.

Appellant notes that in order to establish prima facie obviousness, all of the claimed limitations must be taught or suggested in the prior art. See, e.g., MPEP § 2143.03. To establish a prima facie case of obviousness, in addition to other requirements, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

a. The suggested combination of Jou, et al. with Daniels, et al., Klimant, and Rylatt, et al. fails to disclose or suggest a flow-through assay device wherein the immobilized calibration capture reagent comprises a polyelectrolyte as is required in independent claim 92.

Jou, et al. discloses an assay in which a soluble capture reagent or a soluble sandwich-type complex including the capture reagent, an analyte, and an indicator can be bound through charge interaction in a reaction zone of a test device. Rylatt, et al. and Daniels, et al. also both disclose assays including zones in which an analyte in a test sample can be bound (termed the test zone in Rylatt, et al. and the capture region in Daniels, et al.). Accordingly, even if the teachings of Jou, et al. could be somehow combined with those of Rylatt, et al. and Daniels, et al. to form a working device, the resulting device could possibly include the charge interaction binding scheme of Jou, et al. in the test zone of Rylatt, et al. or in the capture region of Daniels, et al., but this combined teaching does not involve any calibration zone.

Appellant respectfully submits that proper rationale has not been provided that would lead one of ordinary skill in the art from the teachings of Jou, et al., which provides a charge interaction method for binding a labeled analyte in a reaction zone or on a substrate, and then further modify that teaching and provide instead a calibration zone including a calibration capture reagent that is a polyelectrolyte, as is found in claim 92.

C. Only improper hindsight gained from exposure to Appellant's disclosure would lead the person of ordinary skill from Jou, et al., Rylatt, et al., Daniels, et al., and Klimant to the limitations of claim 92.

In fact, the only teaching directed toward utilization of a polyelectrolyte as a capture reagent in a calibration zone is in the captioned application. Clearly, the only

incentive or motivation for modifying Daniels, et al. using the teachings of Klimant, Rylatt, et al., and Jou, et al. in the manner suggested in the Final Office Action results from using Appellant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103. No common sense line of reasoning has been provided that would lead one of ordinary skill in the art from the teachings of Daniels, et al. to the suggested combination with Klimant, Rylatt, et al., and Jou, et al. Only with Appellant's specification could the structure of claim 92 be attained, and any attempt to arrive at the structure of claim 92 through study of the cited references is only reachable from improper hindsight analysis after viewing Appellant's specification.

V. Conclusion

In conclusion, it is respectfully submitted that the claims are patentably distinct over the prior art of record, and that the present application is in complete condition for allowance. As such, Appellant respectfully requests issuance of the patent.

Respectfully submitted,

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8. CLAIMS APPENDIX

1-63. (Cancelled)

64. A method for detecting an analyte within a test sample, the method comprising:

i) providing a lateral flow assay device that comprises a porous membrane in fluid communication with phosphorescent particles conjugated with a specific binding member, the phosphorescent particles comprising a phosphorescent label encapsulated within a matrix, the phosphorescent label emitting a detection signal having an emission lifetime of about 1 microsecond or more following excitation of the phosphorescent label and having a Stokes shift of greater than about 100 nanometers, wherein the porous membrane defines a detection zone within which is immobilized a capture reagent;

ii) contacting the lateral flow assay device with the test sample;

iii) subjecting the detection zone to illumination pulses to generate the detection signal; and

iv) thereafter, measuring the intensity of the detection signal, wherein the amount of the analyte within the test sample is proportional to the intensity of the detection signal.

65. The method of claim 64, wherein the phosphorescent label comprises a metal selected from the group consisting of ruthenium, osmium, rhenium, platinum, palladium, and combinations thereof.

66. The method of claim 64, wherein the phosphorescent label comprises a ligand selected from the group consisting of pyridine, pyrazine, isonicotinamide,

imidazole, bipyridine, terpyridine, phenanthroline, dipyridophenazine, porphyrin, porphine, derivatives thereof, and combinations thereof.

67. The method of claim 66, wherein the ligand is a porphyrin ligand, porphine ligand, or derivative thereof.

68. The method of claim 66, wherein the metal complex comprises a bipyridine ligand or derivative thereof.

69. The method of claim 64, wherein the phosphorescent label comprises platinum (II) coproporphyrin-I and III, palladium (II) coproporphyrin, ruthenium coproporphyrin, zinc(II)-coproporphyrin-I, platinum(II) tetra-meso-fluorophenylporphine, palladium(II) tetra-meso-fluorophenylporphine, derivatives thereof, and combinations thereof.

70. The method of claim 64, wherein the matrix comprises metal oxide particles, polymer particles, or combinations thereof.

71. The method of claim 64, wherein the particles have an average size of from about 0.1 nanometers to about 100 microns.

72. The method of claim 64, wherein the particles have an average size of from about 1 nanometer to about 10 microns.

73. The method of claim 64, wherein the matrix acts as a barrier to protect the phosphorescent label from quenching.

74. The method of claim 73, wherein about 30% or less of the detection signal is quenched when the phosphorescent particles are exposed to a quencher.

75. The method of claim 73, wherein about 20% or less of the detection signal is quenched when the detection probes are exposed to a quencher.

76. The method of claim 64, wherein the phosphorescent label emits a detection signal having an emission lifetime of about 10 microseconds or more.

77. The method of claim 64, wherein the phosphorescent label emits a detection signal having an emission lifetime of about 100 to about 1000 microseconds.

78. The method of claim 64, wherein the intensity of the detection signal is measured from about 1 to about 100 microseconds after the detection zone is subjected to one or more pulses of illumination.

79. The method of claim 64, wherein the capture reagent is selected from the group consisting of antigens, haptens, protein A or G, neutravidin, avidin, streptavidin, captavidin, primary or secondary antibodies, and complexes thereof.

80. The method of claim 64, wherein the illumination is provided by a pulsed excitation source.

81. The method of claim 64, wherein the intensity of the detection signal is measured by a time-gated detector.

82. The method of claim 64, wherein the specific binding member is selected from the group consisting of antigens, haptens, aptamers, primary or secondary antibodies, biotin, and combinations thereof.

83. The method of claim 64, wherein the specific binding member is configured to preferentially bind with the analyte.

84. The method of claim 64, wherein the specific binding member is the same as or an analog of the analyte.

85. The method of claim 64, wherein the porous membrane further defines a calibration zone within which is immobilized a calibration capture reagent.

86-88. (Canceled)

89. The method of claim 85, further comprising subjecting the calibration zone to illumination pulses to generate a calibration signal.

90. The method of claim 85, wherein the calibration capture reagent is capable of binding the phosphorescent particles.

91. The method of claim 85, wherein the calibration capture reagent is capable of binding a calibration probe.

92. The method of claim 85, wherein the calibration capture reagent comprises a polyelectrolyte.

9. EVIDENCE APPENDIX

None

10. RELATED PROCEEDINGS APPENDIX

None